REMARKS

Applicants refer the Examiner's attention to the Supplemental Information Disclosure Statement submitted herewith. Applicants respectfully submit that pending claims 35-38, 45, 46, 49, 55-59, and 65-73 are allowable.

A. Background of Applicant's Invention

Epithelial ovarian cancer is a highly lethal malignancy. It is the fourth leading cause of cancer deaths among women in the United States and causes 140,000 deaths annually in women worldwide. Despite intensive research efforts over the past decade directed towards improved detection and treatment of ovarian cancer, the long-term survival of women with ovarian cancer has only improved modestly. Progress in the fight against ovarian cancer has been hampered by a number of factors, including late diagnosis, the molecular heterogeneity of tumors, the absence of highly curative chemotherapy, and the lack of a valid animal model for the disease.

Routine use of the combination estrogen–progestin oral contraceptive pill (OCP) was known to confer a remarkable 30-50% reduction in the risk of developing subsequent epithelial ovarian cancer. There was a prior widespread belief that the protective effect of oral contraceptive use is due to the ability of these agents to inhibit ovulation, thereby decreasing the amount of genetic damage incurred by the ovarian surface epithelium in OCP users. This belief would suggest that (a) the benefit from the ovarian cancer protective of OCP use would be confined only to young women who are ovulating, with the protective effect dissipating over time; (b) no improvement could be made to OCP formulations to further reduce the risk of ovarian cancer because all OCPs are highly effective at inhibiting ovulation; and (c) post-menopausal women, who by definition do not ovulate and who represent the group of women at

greatest risk of ovarian cancer, could derive no protective effect from post-menopausal administration of the drugs.

1. Discovery Of Progestin As A Chemopreventive Agent

Applicants' research led to an alternative hypothesis: that the well-known protective effect conferred by OCPs against ovarian cancer may be due to potent and direct biologic effects of OCP progestins on the ovarian epithelium. Applicant Rodriguez discovered that the progestin component of the OCP functions as a classic chemopreventive agent, by activating well-known chemopreventive molecular pathways in the ovarian surface epithelium. Specifically, in a study involving primates, applicant discovered that progestins markedly induce programmed cell death (apoptosis). Apoptosis has been strongly implicated in cancer prevention *in vivo*. Applicant conducted further laboratory and animal research. The results of that research supported the discovery that progestin acted as a classic chemopreventive agent.

Later analysis of human data also supported this conclusion. Data was analyzed from the Cancer and Steroid Hormone (CASH) study, a large case control study involving over approximately 400 women with ovarian cancer and 3000 matched controls. The analysis demonstrated that older progestin-potent OCP formulations conferred twice the reduction in ovarian cancer risk as compared to the newer lower progestin potency OCPs, irrespective of estrogen content and duration of use. The analysis demonstrated ***a significant reduction (60-70%) in risk of ovarian cancer associated with exposure to high progestin potency OCPs,*** even among women who used OCPs for a relatively short duration (less than 18 months). A paper on this analysis was published in the *Journal of the National Cancer Institute*, Vol. 94, No. 1, on January 2, 2002. Our data demonstrate that ***lowering the progestin dosage*** in the newer OCPs has caused a ***marked reduction in ovarian cancer protection***.

2. Vitamin D

The finding that progestins activate the apoptotic molecular pathway raised the possibility that other agents that could similarly activate cancer preventive pathways in ovarian epithelial cells. Applicants studied Vitamin D and discovered that it has potent biologic effects pertinent to cancer prevention in epithelial cells, including induction of apoptosis, differentiation, and TGF-β.

Applicants' discovery can allow the design of various pharmaceutical products for highly effective chemoprevention of ovarian cancer, such as OCP products, as well as products directed to women of all ages, including post-menopausal women. The use of Vitamin D, rather than a high dose of progestin, would allow one to obtain a high level of ovarian cancer protection without any of the concerns relating to potential side effects that might be associated with higher levels of progestins. In other words, by discovering that Vitamin D can activate the apoptotic pathway of ovarian epithelial cells, one can combine Vitamin D with a progestin, with both being at relatively low dosages, and still obtain the high level of protection against ovarian cancer.

B. The Need Reference Teaches Away From Applicants' Invention

The Examiner rejected claims 35-39, 41, 42, 45, 46, and 55-59 as unpatentable over the abstract of the Need et al. reference. The Examiner states that the abstract of the Need et al. reference teaches the combination of ovarian hormones (specifically norethindrone) and a vitamin D compound (specifically calcitriol). The Examiner rejected Applicants' composition claims as obvious over the Need reference. Applicants submitted a copy of the full Need reference for consideration along with the abstract.

Applicants submit that the instant claims fall into three different broad categories

for purposes of responding to this Office Action. The first group of claims (35-44) is drawn to ***single unit dosages*** containing a progestin and a Vitamin D compound. The second group of claims (45-54) is drawn to compositions that are ***contraceptively*** effective. The third group of claims (55-73) is drawn to ***hormone replacement therapy*** regimens for administration to post-menopausal women. Applicants have amended the third group of claims to include dosages of Vitamin D that are far higher than the dosages found in the Need reference as described below.

The Need reference does not anticipate any of the pending claims. Thus, there is no rejection under 35 U.S.C. §102. Rather, the rejection is one of obviousness under 35 U.S.C. §103. However, in order to be held to be obvious using a single reference, there must be a motivation to modify the teachings of a reference to arrive at the claimed invention. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed.Cir. 2000). However, neither the Need abstract nor the full Need reference provide any such motivation to arrive at the claimed subject matter here. Rather, Need teaches away.

The full Need reference shows that the study involved the administration of ***separate*** pills of various compounds. Two of those compounds were a ***separate pill*** of progestin hormone and a ***separate*** pill of Vitamin D compound. Need administered the separate pills in various combinations to post-menopausal women with osteoporosis to determine if there was a benefit from the various therapies, including some combination therapies. With respect to combining progestin and Vitamin D, Need found that there was absolutely no benefit.

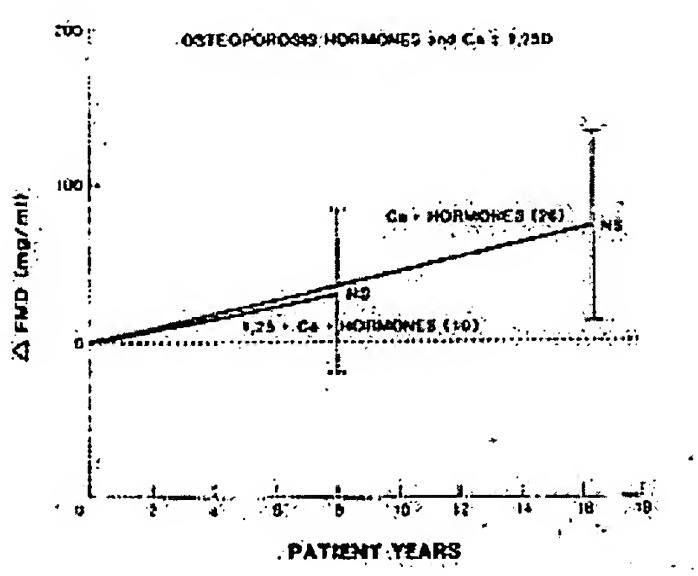
First, as stated in the Need abstract, Need combined (1) calcium with progestin and compared the results to (2) the combination of Vitamin D, calcium and a progestin hormone. The abstract of the Need reference states that there was no benefit to combining Vitamin D with progestin: "[c]alcium and ovarian hormones ***with or without calcitriol***, caused a small non-

significant rise in forearm mineral density." In other words, one obtained the "small non-significant rise in forearm mineral density" by just combining calcium with progestin.

In fact, as shown in the full Need reference, the numerical gain in bone density for "calcium plus progestin" is slightly higher than "calcium plus vitamin D plus progestin," although not significantly so:

> There was a non-significant gain of bone in each of the two groups who received hormones together with calcium (+4.4 ± 5.2 mg/ml/yr) or calcitriol (+3.9 ± 6.4 mg/ml/yr; Fig. 2).

(Need et al. at p. 277). This is shown graphically in Figure 2, reproduced below, where the "Ca + HORMONES" is slightly higher than "1,25 + Ca + HORMONES":



(*Id.*).

As seen in Figure 2 of the full Need reference, the combination of progestin with calcium showed some slight benefit. However, there was no added benefit when Vitamin D was added to the progestin/calcium combination (see Figure 2 above). Thus, Need teaches no benefit of combining progestin with Vitamin D. Without any benefit to the combination, one would certainly have no motivation to use these combined products any further. More specifically, Need would provide no motivation to use it in any way as shown by the three categories of claims that are discussed below.

1. Need Does Not Teach Or Motivate Single Unit Dosages And Thus Does Not Render Obvious The First Group Of Claims (35-44)

Applicants submit that the first group of claims requiring single unit dosages (claims 35-39, 41, and 42) are not obvious over the Need abstract or the full Need reference. As an initial matter, the Need reference absolutely does not teach a ***single unit dosage*** containing a progestin and a Vitamin D compound as required by the claims. Thus, Need could only render these claims obvious if it provided some motivation to take the further, undisclosed step of combining a progestin and a Vitamin D compound into a single unit dosage. Because there was no benefit shown in the Need study from combining progestin and Vitamin D, there would be no motivation to combine the compounds into a single unit dosage; thus, the first group of claims regarding single unit dosages would not be obvious.

2. Need Does Not Teach Or Even Suggest Contraceptively Effective Compositions And Thus Does Not Render Obvious The Second Group Of Claims (45-54)

Applicants also submit that claims 45 and 46, from the second group of claims, are not obvious under the Need reference because the instant claims are drawn to compositions that are contraceptively effective. The combinations in the Need study were administered as hormone replacement therapies to post-menopausal, non-ovulating women whose average age was 61.5 to 65.7 with a SEM of +/- 1.5-2.5 years. The combinations were being tested for their efficacy in increasing bone density for such women. Therefore, there would be no motivation from the teaching of make ***contraceptively*** effective combinations. Thus, the second group of claims regarding regimens that are contraceptively effective are not obvious under Need.

3. Need Does Not Teach The Increased Dosages Of Vitamin D That The Third Group Of Claims (55-73) Are Drawn To And The Applicants' Claims Are Therefore Distinguishable

Applicants submit that claims 55-59, part of the third set of claims regarding hormone replacement therapy, are not obvious and to the extent the claims were anticipated, they have been amended. Applicants submit that the third group of claims are distinguishable from the Need reference because Need does not teach the use of a vitamin D compound with progestin alone. Need teaches a vitamin D compound with calcium and vitamin D with calcium and a progestin. Need shows no added benefit of adding progestin to the vitamin D and calcium composition in the studies on post-menopausal women. Therefore, there would be no motivation from Need to use vitamin D and progestin only in such a population.

In addition, Applicants submit that there would be no motivation from Need to increase Vitamin D dosages to the levels in the amended and newly presented claims if adding vitamin D did not provide an additional benefit to non-ovulating women. Applicants submit that their Vitamin D dosages are significantly higher than the dosages used in the Need study. For the claims measured in mg/kg, the dosage ranges of the amended claims would all fall within 0.006 mg and 60 mg (assuming the average weight of a woman is 60kg)—much greater than the 0.25 microgram (0.00025 mg) dose of Vitamin D in the Need reference. Claims 67-73 for dosages in I.U. are also much greater than 0.25 microgram dose in Need.

Please charge any fees associated with this Amendment to Deposit Account No. 18-1942.

Respectfully submitted,

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